

Exercise, inflammation and acute cardiovascular events.

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ABSTRACT

Individuals who participate in regular exercise over time have a markedly reduced risk of cardiovascular disease. Paradoxically, in susceptible individuals with underlying, often undiagnosed, disease states, exercise may acutely increase an individual's risk of cardiovascular events during and immediately following physical exertion. Exercise is thought to evoke conditions that trigger atheromatous plaque rupture or trigger life threatening arrhythmias in individuals with pre-existing, vulnerable coronary artery and inherited cardiovascular disease respectively. This transient increased risk may be driven by the inflammatory trigger provided by physical exertion where exercise is associated with an upregulation of inflammatory mediators in the acute phase. Conversely, habitual exercise can lead to a modulation of the inflammatory response over time. This review explores: exercise related inflammation; acute cardiovascular events related to exercise and strategies to mitigate these risks.

Keywords: Athlete's heart, acute cardiovascular events, exercise immunology.

INTRODUCTION

The benefits of exercise for cardiovascular health are well recognised. The biggest leap in benefit comes to those that change from no physical activity to modest forms of activity such as brisk walking (1-4). However, the dose-response curves are not fully understood; particularly in those that participate in exercise far above national recommendations (150-300 minutes of moderate-intensity, or 75-150 minutes of vigorous-intensive aerobic activity per week) such as elite athletes (3, 5-7). There is no evidence that healthy individuals participating in exercise are at an increased risk of cardiovascular events. However, in those with susceptible disease states, exercise may provide the inflammatory, haemodynamic and autonomic trigger needed for a cardiac event such as sudden cardiac death (SCD).

This review will explore selected inflammatory responses induced by exercise, their relationship with acute cardiovascular events and strategies that have been outlined by international guidelines in mitigating these events.

ACUTE CARDIOVASCULAR EVENTS

There is a large variation in the estimates of SCD during sport, and it appears that these risks are not homogenous as individuals with susceptible disease states appear to carry a greater burden of risk.

The general population

Overall, the rate of cardiac events in healthy individuals participating in sport is low. In the general population, the incidence of cardiac arrest in 12-45 year olds participating in sport is estimated to be 0.76/100,000 person-years and 0.3/100,000 in those aged 10-90 years (8-10). Based on two large SCD studies assessing out-of-hospital cardiac arrests, the American Heart Association (AHA) report annual incidence rates of 0.5-5.5 and 0.04-0.3 per 100,000 individuals in males and females respectively (10-12). The Registre des Accidents Cardiaques lors des courses d'Endurance reported 17 life-threatening events in 551,880 long distance runners, of which two were fatal (13). While the overall incidence is low, these data suggest that there is heterogeneity in the risk of SCD in exercise which is driven by susceptibility in subpopulations.

There are significant limitations to these data. Capturing sport related SCD is difficult, as it will undercount events in

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those performing non-organised, casual sport and elucidating cardiovascular versus non-cardiovascular causes of death can be difficult without autopsy. Furthermore, specific groups are underrepresented in the sports cardiology literature; up to half of published data exclude female participants altogether and non-white individuals have a lower rate of representation when compared to individuals of white ethnicity in other areas of cardiovascular research (14-16).

Susceptible individuals: atherosclerosis versus inherited cardiac disease

Individuals susceptible to acute cardiovascular events during exercise can be generally divided by age. One, young individuals (under 35 years) with inherited cardiac disease such as hypertrophic cardiomyopathy (HCM). Two, older individuals (above 35 years) with underlying atherosclerotic disease. This effect is seen in contemporary data. The FIFA Sudden Death Registry noted that the most common cause of SCD in players above 35 years was coronary disease, whereas in those under 35 years, sudden unexplained death (22%), cardiomyopathies (18%) and other causes (21%) accounted for most deaths (17, 18). Importantly, the incidence of SCD related to exercise appears to be higher in the above 35 years group (3.0 per 100,000 individuals compared to 0.3 per 100,000 in individuals under 35 years) (10, 11). When considering the risks of acute cardiovascular events, these two groups should be discussed separately as the processes of identifying and managing risk may be distinct.

SCD and exercise prescription in inherited disease states

Whilst rare, sudden events in the young tend to receive significant media focus, especially when occurring in apparently healthy individuals in high-profile events. Cardiac arrest and death can be the first presentation of underlying disease such as cardiomyopathy, even in individuals subject to pre-participation screening. Although media focus has centred around the incidence of SCD in organised competition, the risks of acute cardiovascular events are not reserved for those competing at elite level and a higher absolute number of exercise related SCD are observed in non-competitive events (11, 19).

The AHA Council Scientific Statement from 2007 reported HCM and other congenital disease to be the most common cardiac cause of SCD in young athletes (1-51%), usually triggered by ventricular arrhythmias (20, 21). However, more recent data suggests that a large proportion of young athletes with SCD have a structurally normal heart (8, 11). Furthermore, most individuals with HCM do not die during or immediately following exercise. Up to 85% of all HCM related SCD occurs during sedentary activity or rest (22). Similarly, another study found that only 33% of cardiac arrests in individuals with HCM occurred following vigorous physical activity, 43% occurred during daily activities and a further 24% during rest or sleep (23).

Due to the previously perceived risk of SCD associated with exercise, individuals with inherited disease such as HCM have traditionally had conservative exercise recommendations (24). However, the pitfalls of exercise abstinence in HCM are being increasingly recognised and recent studies have investigated the role of exercise prescription in individuals with HCM, as it may improve both cardiorespiratory fitness and arrhythmia burden (8, 24). One study enrolled 20 individuals with symptomatic HCM into a

supervised exercise programme (25). The investigators showed an increase in functional capacity (4.7 to 7.2 metabolic equivalents) and an improvement in at least one New York Heart Association functional class in 50% of the group, with no concomitant increase in adverse cardiac events (25). As the risk of arrhythmogenesis in HCM is thought to be driven by an acute rise in catecholamines, studies have investigated the characteristics of the adrenergic response. In nine individuals with non-obstructive HCM, a cardiopulmonary exercise study showed that catecholamine levels remain stable during moderate exercise intensity, but increased at higher intensities (26). The authors suggest that cardiopulmonary exercise testing could be a tool used in exercise prescription in individuals with HCM (26). Further trials are underway to evaluate the role of exercise in HCM (ClinicalTrials.gov NCT03335332). Importantly, this may not apply to all types of cardiomyopathy and some studies suggest that in arrhythmogenic right ventricular cardiomyopathy, exercise can accelerate disease progression and trigger arrhythmia (11, 27, 28).

Atherosclerotic disease

In older individuals with underlying atherosclerotic disease, exercise may be associated with a transient rise in the risk of acute myocardial infarction (11, 29). Estimates of the relative risk and odds ratio of myocardial infarction following strenuous physical activity are between 1.1 to 5.7 when compared to very light or no exertion (29-32). In 849 individuals with acute myocardial infarction, 14.1% were triggered by moderate physical activity (33). In adults with coronary artery disease, the wall stress precipitated by tachycardia and transient hypertension can cause extension of existing coronary plaque fissures, catecholamine mediated platelet aggregation and more rarely, coronary artery spasm in unhealthy segments, (20). As the population ages, endurance exercise will be taken up by older individuals. Age is an independent driver of atherosclerosis, and the rise in participation is unlikely to be restricted to individuals free of underlying cardiovascular disease. It remains to be seen whether this will be reflected in a rise in acute cardiovascular events during exercise (34).

INFLAMMATORY RESPONSE TO EXERCISE

Acute inflammation as a response to exercise

Exercise is a 'stressor' activity. Over time, repeated cycles of damage and repair can improve cardiorespiratory fitness. In the acute setting, the 'acute phase response' (APR) to exercise describes the release of pro-inflammatory and anti-inflammatory mediators, including cytokines (35) (Figure 1, Table 1). These rises are transient, and likely determined by the intensity and duration of the exercise, alongside the physiological reserve, including training history of the participant. Siegel et al assessed inflammatory and haemostatic markers in apparently healthy marathon runners who did not take anti-inflammatory medication (36). They compared pre-race measurements against values taken four hours after race completion. Increases were seen in C-reactive protein (CRP), von Willebrand factor, D-dimer and fibrinolytic activity, with a concurrent reduction of fibrinogen (36). In a separate cohort, they demonstrated an increase in white blood cell and platelet counts, with a shortened time to aggregation (36). Von Willebrand factor, D-Dimer and white blood cell count remained elevated the following morning (36). Studies have shown CRP

rise following vigorous physical activity(35). The increase in CRP is thought to be predominantly mediated by interleukins (IL).

IL-6

IL-6 is the initial cytokine released in response to exercise and demonstrates the highest rise but is dependent on the duration, intensity and level of muscle mass recruited in physical exertion and peaks upon completion of the activity (35, 37-39). In vivo, IL-6 is predominantly produced by monocytes, macrophages, fibroblasts, endothelial cells and skeletal muscle, in response to exercise-related muscle injury (39, 40). It was thought that IL-6 is a pro-inflammatory cytokine and is found elevated in states of chronic low grade systemic inflammation, and disease states such as congestive cardiac failure, where it is implicated in myocardial dysfunction and has been shown to predict mortality in females ≥ 65 years with cardiovascular disease (41-44). However, more contemporary evidence suggests that the rise in IL-6 is due to its anti-inflammatory role in acute exercise. This occurs through its antagonistic relationship with the inflammatory marker, tumor necrosis factor alpha (TNF- α)(37, 43).

TNF- α levels can predispose individuals to endothelial dysfunction, atherosclerosis and extenuate the progression of heart failure(45). TNF- α is found in higher concentrations in diabetes, increasing age, increasing atherosclerosis and predicts mortality(45-47). Whereas insulin sensitivity is improved by IL-6, TNF- α antagonises this effect(37). These moderate increases in IL-6 in response to acute exercise deliver anti-inflammatory effects by opposing TNF- α and stimulating IL-1ra(37, 43). The rise in IL-6 seen in exercise differ to that seen in acute pathological states such as sepsis, as there is no concomitant rise in other markers such as TNF- α and IL-1 β (37, 43). However, the rise in IL-6 may not be a homogenous phenomenon to all exercise types. A recent systematic review assessing the change in inflammatory markers in response to moderate and intense exercise demonstrated variable conclusions(48). IL-6 was assessed in 13 of these studies and six studies did not report a significant rise in IL-6 following exercise (48). Stelzer et al and Connolly et al showed a rise in IL-6 in moderately trained amateur athletes and non-competitive men respectively (49, 50). Conversely, there were no changes in IL-6 after exertion in eight endurance athletes(51). These results suggest that the rise in IL-6 may be determined by the type, intensity and duration of exercise.

While IL-6 may have a systemic anti-inflammatory role, it is unclear if this effect confers cardiac protection. IL-6 has been implicated during the inflammatory phase of acute coronary syndromes and associated with haemostasis dysfunction in animal studies (52). García-Salas et al showed that IL-6 predicted adverse events in individuals with non-ST elevation acute coronary syndrome (53). IL-6 is also thought to destabilise atherosclerotic plaques, activate cellular adhesion molecules, have a role in myocardial ischaemia-reperfusion injury and has been investigated as a drug target for reducing inflammation in coronary syndromes (54-57). This rise of IL-6 with exercise appears to correlate with the period of increased susceptibility. Therefore, questions remain whether IL-6 is a potential agent in triggering acute cardiovascular events, particularly in individuals with susceptible disease states. Further studies are needed to investigate causality.

Markers of myocardial injury

Endurance exercise is associated with a transient rise of serum markers traditionally attributed to myocardial injury, including troponin and brain natriuretic peptide (BNP). Meta-analyses have suggested that this may be a common phenomenon (58, 59). Some argue that brief rise and fall of troponin may reflect augmented myocyte permeability that releases free circulating troponins into the extracellular space in response to several mechanisms including inflammation (58, 60). Mousavi et al performed cardiac magnetic resonance (CMR) imaging and biomarker analysis immediately following the completion of a marathon in 14 individuals (61). Not only were myocardial proteins such as troponin, creatine kinase and myoglobin raised, but they demonstrated a reduction in right and left ventricular function. However, there was no evidence of late gadolinium-enhancement on CMR, which led the authors to conclude that a rise in cardiac biomarkers may be attributable to release from the cytosol rather than an indication of myocardial necrosis (61). This view is supported by the characteristics of the rise and fall of troponin following marathon running in other studies, where authors have suggested that biomarker elevation reflects alternative myocardial metabolism (62). Factors that determine the magnitude of this rise are not clear but may be associated with both athlete-related and exercise-related characteristics. For example, Leckie et al assessed the rise in high-sensitivity troponin following a marathon in apparently healthy individuals, individuals with pre-existing heart disease and those who have collapsed at the finish line (63). They found there to be an asymptomatic rise in troponin that correlated with pre-race troponin within the control group (63). Other studies have demonstrated heart rate during exercise to be a predictor of troponin rise following exercise (64). It remains to be seen if the relationship between an individual's training history and current participation may drive the associations that have been observed. More recent data cast doubt on exercise induced troponin rise being a benign event. Aengevaeren et al assessed troponin I in 725 older long-distance walkers (65). They found that a rise in troponin I greater than the 99th percentile predicted mortality and cardiovascular events(65). While clinical and mechanistic conclusions remain speculative at present, it may suggest that troponin elevation is not a benign phenomenon in some groups following exercise.

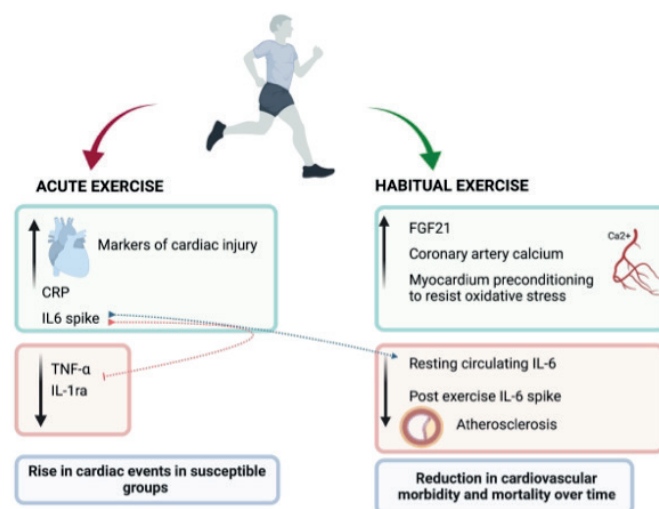


Figure 1. Inflammation related to acute and habitual exercise

Adrenergic surge

Alongside traditional markers of inflammation, the hypothesised mechanism of SCD in diseases such as HCM are thought to be caused by an adrenergic surge. Some argue that there is a higher burden of SCD in sport types with adrenergic surge, such as football and basketball (66, 67). Intense physical activity can trigger the sympathetic nervous system and cause a rapid increase in circulating catecholamines (68). It is thought that this adrenergic surge, increased sympathetic drive, myocardial stretch and microvascular ischaemia can potentiate the risk of arrhythmia, and may be a cause of death in individuals with HCM (8, 69). Catecholamines stimulate both α - and β -adrenoreceptors (70). A subsequent rise in intracellular Ca^{2+} , coronary artery spasm and myocardial ischaemia can increase the risk of malignant arrhythmogenesis (70).

Habitual exercise modulates the inflammatory response

Habitual exercise may lead to regulation of the APR through immunomodulation, upregulation of antioxidative mediators and overall reduction in oxidative stress (71). After prolonged periods of exercise, the distribution profile of inflammatory cytokines, such as IL-1, IL-8 (pro-inflammatory), IL-2, IL-4, IL-10, IL-13 (anti-inflammatory), is balanced towards those with anti-inflammatory properties (71). Periods of exercise may also upregulate the expression of markers associated with favourable cardiac phenotypes. For example, fibroblast growth factor 21 (FGF21) may offer protection against cardiac fibrosis following an MI. In an animal study, exercise training increased FGF21 protein expression and led to improvements in cardiac function by mitigating cardiac fibrosis (72). In mice with ligation of the left anterior descending coronary artery inducing an MI, exercise promoted FGF21 pathways (73).

Over time, physical activity promotes a number of cardioprotective mechanisms including: autonomic sympathetic modulation, a reduction in circulating angiotensin II and upregulation of apelin (74). Animal studies have demonstrated that exercise may mediate cardioprotective effects through a reduction in pro-inflammatory cytokines, reactive oxygen species, superoxides and preconditioning of the cardiac muscle to oppose oxidative and heat stress (75, 76). The role of these inflammatory mediators in cardiovascular inflammation is not fully understood during and following exercise. Whilst interleukins and mediators such as $\text{TNF-}\alpha$ may be implicated in the 'response-to-injury' pathway, leading to atherosclerosis progression, further research is needed to explore possible causal links between acute phase inflammatory mediators released in response to exercise and the development of cardiovascular events in athletes (34).

Over time, this modulation in inflammation may protect against disease processes such as atherosclerosis, where exercise can exert anti-inflammatory effects on the endothelium (58, 77). Exercise can upregulate the production of vasodilator molecules and inhibit the expression of oxidative species (58, 77). This view is supported by evidence that habitual exercise is associated with a reduction in the progression of atherosclerosis, and it is widely accepted that exercise promotes coronary artery health. Habitual exercise may modulate the platelet activation seen immediately following exercise, where studies have shown that platelet activation is seen in sedentary subjects but not in physically active subjects (78, 79). Further still, animal studies have shown

that exercise may modulate the inflammatory response, such as $\text{TNF-}\alpha$ and IL-6 IL-1 β , following induced myocardial infarction (80). However, contemporary data suggest that the relationship between exercise and coronary physiology is not fully understood. In 25,485 individuals, when compared to individuals who were inactive, higher levels of physical activity were associated with a more rapid progression of coronary artery calcium (81). This effect was only observed in individuals who had atherosclerosis at baseline, and not seen in individuals who had no detectable coronary artery calcium (81). This finding is consistent with other studies that have demonstrated that athletes had a higher prevalence of atherosclerotic plaques when compared to sedentary individuals; largely comprising of calcified plaques, whereas sedentary individuals harboured plaques of mixed morphology (82). The prognostic implications of these findings remain unclear. On one hand, they could be interpreted to be a pathological consequence of exercise but on the other, they could reflect a more stable plaque that protects against acute coronary syndrome. In the pathogenesis of acute coronary syndromes, it is the rupture of a thin fibrous cap and plaque erosion that account for a large proportion of acute coronary syndromes that cause death (83). Erosion of the calcified nodule and intraplaque haemorrhage only account for a small proportion in comparison (83). It may be that calcified plaques offer biomechanical stability, preventing cap rupture in response to increased wall shear stress or the acute inflammatory response. This view may be supported by molecular imaging studies which have demonstrated that plaque calcification may be a protective response to chronic inflammation, as it stabilises otherwise thin plaques that can predispose vessel occlusion through exposure of the necrotic core and thrombosis (84). Interestingly, the systemic inflammation following a myocardial infarction can itself trigger the onset of further metalloproteinase activity; which can trigger events in non-culprit plaques by catalysing collagen breakdown, while T-cells secrete interferon- γ that can inhibit further production of collagen, leaving the fibrous cap of a plaque at risk of rupture (83, 85). This may be why we observe the risks of further infarction in non-culprit lesions to be decreased when revascularisation is performed during the immediate phase of a myocardial infarction (83). This is important in the context of pro-inflammatory events such as exercise, as they may trigger the rupture of prone plaques (11, 86).

Despite many published studies, the limitations in assessing myocardial inflammation should be recognised. Typically, inflammation is measured through serum markers of inflammation and necrosis such as IL-6, $\text{TNF}\alpha$, troponin, high sensitivity C-reactive protein and fibrinogen (43, 87). However, the rise in these markers are not specific to the myocardium (88, 89). Similarly, CMR techniques to assess for oedema, pericardial effusion, hyperaemia (early gadolinium enhancement) and necrosis (late gadolinium enhancement) are not specific to inflammation and the spatial resolution of the technique is relatively limited and so smaller myocardial defects may remain undetected (88, 90). Invasive methods such as an endomyocardial biopsy are not routinely performed and difficult to justify in the context of clinical research, particularly in apparently healthy individuals. Novel methods such as ultrasmall superparamagnetic particles of iron oxide on CMR may help to elucidate inflammatory processes such as macrophage infiltration in the future (88).

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Acute response to exercise		Inflammation assessed	Key, selected results
First author, date	Participants/exercise type		
Siegel et al (36)	Marathon runners	Biomarkers including: CRP, von Willebrand factor, D-dimer, fibrinogen, fibrinolytic activity, white blood cell. Samples collected morning before, within 4 hours of marathon completion and morning after the race.	- Increase in CRP, von Willebrand factor, D-dimer, fibrinolytic activity and WBC increased within 4 hours of marathon completion when compared to baseline.
Mousavi et al (61)	Marathon runners (n=14)	Biomarkers including: myoglobin, creatine kinase, cardiac troponin T. Samples collected at baseline, immediately after the race, at the time of cardiac imaging and one week following completion. CMR performed at baseline and within three days of marathon completion	-Myoglobin, creatine kinase, and troponin levels were raised following completion of the marathon but normalised after one week. -Right ventricular end-diastolic diameter, end-diastolic area and endo-systolic area increased following completion. - No evidence of delayed enhancement of the left ventricle.
Siezel et al (49)	Moderately trained amateur athletes, endurance cycling(n=7)	Biomarkers including: IL-6, Fibrinogen, creatine kinase, NT-pro-BNP. Samples collected: 2 days before competition, and within 15 minutes of completion.	-IL-6 and fibrinogen increased following race completion. -NT-pro-BNP, creatine kinase, creatine kinase-MB increased following race completion.
Aengevaeren et al (65)	Walkers (30-55km) (n=725)	Cardiac troponin I. Clinical outcomes include: all-cause mortality and major adverse cardiovascular events. Samples collected: at baseline and within 10 minutes of walking completion.	-Significantly lower survival in individuals with post-exercise troponin I >0.040 ug/L compared with ≤0.040ug/L (HR: 3.21 95%CI=1.79-5.77) in multivariable models. This remained significant when adjusted for baseline troponin.
Response to habitual exercise			
Fischer et al (115)	Healthy untrained males (n=7). 10-week knee extensor endurance training.	IL-6 mRNA expression. Samples collected at rest, end of exercise and two hours after rest.	-Exercise capacity increased. -IL-6 mRNA increased acutely from baseline to post-exercise. However, after the 10-week training period, skeletal IL-6 mRNA expression only increased 8-fold; compared to 76-fold prior to the training period.
Hamer et al (116)	Whitehall II population (n=4289), self-reported physical activity.	Biomarkers including: CRP, IL-6, Baseline markers collected in phase 3 of the study in 1991-93 and compared at phase 7 of the study 2002-04 giving a mean follow-up of 11.3 years.	-Individuals who showed high adherence to physical activity guidelines had lower CRP, IL-6 at follow-up when compared to those who rarely adherence to physical activity guidelines. Individuals who increased their physical activity also showed lower CRP and IL-6 levels when compared to individuals who were stable.

Table 1. Selected studies assessing inflammation in response to acute and habitual exercise.

MITIGATING ACUTE CARDIOVASCULAR EVENTS DURING AND AFTER EXERCISE

Due to the lack of randomised controlled trials and the relative low number of events, there are no data that identify high-risk exercise and subsequent exercise prescription to mitigate acute cardiovascular events, particularly in healthy individuals (20). The issue is further complicated as exercise is not limited to healthy groups or elite athletes. The following section discusses some general recommendations that international guidelines have offered.

Screening

Pre-participation screening is a vast area of discussion and recent updates are outlined in the 2020 European Society of Cardiology (ESC) Guidelines on sports Cardiology (18). Screening programmes aim to identify individuals at risk and offer strategies to reduce this risk, one of which is exclusion from competition. The drive has been to improve the sensitivity and specificity of pre-participation screening programmes in young athletes (18). There is less focus on screening asymptomatic individuals above 35 years, with screening for ischaemia reserved for those with symptoms or those calculated to be at high risk of coronary artery disease by ESC Systematic Coronary Risk Evaluation (SCORE) (18). There are also areas where international guidelines differ. For example, the European guidelines recommend the use of electrocardiograms in the pre-participation screening protocol, whereas the AHA do not (11, 18, 91).

Exercise prescription: gradual progression of training load

Matching workload to training history to activity may be important. Mittleman et al interviewed 1228 individuals with recent myocardial infarction (92). Around 1 in 20 reported heavy exertion in the preceding one hour before myocardial infarction. They also showed that the risk of myocardial infarction during exercise was higher in individuals who were habitually sedentary (92). Other studies also demonstrate that a disproportionate number of cardiovascular events occur in those with a low-training history participating in unfamiliar levels of physical activity (11, 20, 92). International guidelines recommend that training plans should involve incremental increases in training load, as this theoretically improves an individual's conditioning, reducing their risk of acute adverse events (11, 20).

Warm-up/cool down

Warm-up and cool-down routines are recommended, particularly in those with pre-existing cardiac disease (11). Barnard et al assessed 44 asymptomatic males with and without prior warm-up to vigorous exercise (93). Abnormal ECG patterns were observed in 31 individuals when no prior warm-up was performed, 19 of which showed ischaemic changes, whereas no ECG abnormalities were detected when subjects performed incremental increases in exertion levels (93). They separately demonstrated similar findings in 10 healthy men who performed sudden treadmill exercise without warm-up, where three individuals had ST segment depression and a further three had minor ischaemic changes. While experimental data assessing the prognostic value of warm-up routines is unclear, it is thought that sudden intense physical activity could provide conditions for acute cardiovascular events in individuals at-risk.

Avoiding extremes of temperature

In general, the AHA recommend that inactive individuals and those with cardiovascular disease should reduce vigorous physical activity in extremes of temperature (11). Studies report a higher number of cardiovascular events during and after snow-fall periods, with up to 7% of admitted acute coronary events in those involved in snow shovelling (94, 95). This may be a consequence of training history and activity mismatch or due to angina caused by coronary vasoconstriction in response to cold temperatures (20). Exercise at hot temperatures is associated with relative tachycardia, due to the thermal load and peripheral vasodilation causing a drop in total peripheral resistance (20). Higher temperatures can precipitate dehydration and electrolyte disturbances, which endurance athletes may be prone to (96).

Recognition of symptoms for professionals and patients

SCD can be the first presentation of underlying cardiovascular disease (97). This is particularly evident in young athletes with cardiomyopathies (97). However, in a prospective cohort of athletic individuals with cardiac arrest between the age of 5-34, up to 29% reported symptoms prior to the arrest and 14% were associated with exertion (98). In a retrospective analysis of 60 sudden deaths among squash players, 45 stated symptoms in the week preceding sudden death, with the most common symptom being chest pain (99). International guidelines recommend that individuals that experience cardiovascular symptoms during exercise should cease physical activity and receive medical review (11, 18). Policy makers may wish to focus on education to participants, coaches, families and school teachers and promote the discussion that cardiovascular symptoms, particularly when associated with exertion, should prompt cessation of activity and medical evaluation.

The role of pharmacological prophylaxis

Studies have suggested that there may be a theoretical role for pharmacological prophylaxis in susceptible individuals (11). Siegel argues that marathon runners may be a subpopulation who are at an increased risk of cardiovascular events during activity periods, and as such may warrant aspirin therapy (100). Siegel points to alterations of platelet granularity and clumping during marathon races as evidence of platelet activation during exercise (100). As aspirin irreversibly inhibits cyclooxygenase-1, subsequently decreasing platelet aggregation through thromboxane A2 modulation, they argue that there may be a primary prevention role in these individuals (101, 102). However, the benefits of aspirin are not homogenous to all population and must be carefully assessed against potential bleeding risks observed in several sub-populations, which is a particular concern in athletes engaged in sport with an increased risk of falls and traumatic injury (103, 104). Currently, the role of prophylactic pharmacotherapy for the prevention of exercise related cardiac events remains speculative and is not recommended (11).

The role of recovery and detraining

The role of recovery and detraining in sports cardiology is generally reserved for diagnosis and treatment of cardiovascular disease. In those with cardiac phenotypes that lie in margins of diagnostic overlap between the athlete's heart and cardiomyopathy (termed the 'grey zone'), detraining may be used to assess regression of ventricular size and wall thickness that may point towards a diagnosis of athlete's heart. In non-clini-

cal practice, recovery is an important aspect of athlete training. Training regimes adopt the functional overreaching principle which sees repeated exercise and subsequent temporary loss in performance followed by a period of rest in the hope that improvements in performance follow. There is little to no data that examines the role of rest in the prevention of acute cardiovascular disease during exercise, beyond the principles of gradual acclimatisation to vigorous activity previously discussed. Clinically, there are areas to explore. The window of immunodepression refers to a transient drop in immunological function in response to exercise, determined by a drop in salivary IgA, natural killer cells and antibody production (105, 106). Periods of repeated exercise may increase the exposure to the window, leading to an increased propensity to develop infections (106). This is compounded when paired with health-related behaviour that increases the risks of infection in athletes such as: travel for competition, training in extreme weather and close human contact (107). Inflammatory processes caused by infections, such as community acquired pneumonia, can increase susceptibility to cardiovascular disease (108). These questions have come into light during the coronavirus disease 2019 (COVID-19) pandemic, as there have been some reports of its association with myocardial injury and myocarditis (109). The general recommendations are that athletes with viral infections should refrain from activity during the acute phase of illness and should be asymptomatic before restarting (110). Even so, there is little data that explores the rates of acute cardiovascular events in the acute illness phase. For athletes, where detraining and commitment to teams and sponsors are important aspects of career progression, further data is important to guide recommendations around rest in acute phases of illness. Beyond acute illness, it is also unclear how rest and recovery can help mitigate the risks of acute cardiovascular events during exercise and how it may modulate exercise related inflammation, particularly in healthy individuals who engage in regular exercise.

Urgent treatment

Although beyond the scope of this review, a key strategy to improve outcomes in the setting of organised sport participation is to ensure the prompt delivery of resuscitation. In the setting of cardiac arrest, this occurs through cardiopulmonary resuscitation and automated external defibrillators (AEDs). In an 18-year observational study, it was reported that neurologically intact survival rates in sports centres with AEDs was 93% compared to 9% in centres without ($p < 0.001$) (111). In this study, the availability of an onsite AED was the only independent factor that predicted survival. A recent systematic review showed that in 78% of cases, sports related arrests present with a shockable rhythm (112). Moreover, both bystander cardiopulmonary resuscitation and AED use were associated with survival following exercise related SCD (112). As such, there is a growing need for not only the integration of AEDs in professional and non-professional sport settings, but also improved training in staff and the community (113, 114).

CONCLUSIONS

Exercise evokes an acute inflammatory response that may be a trigger for acute cardiovascular events, but this is rare in those without underlying disease. This is characterised by the release of cytokines and biomarkers associated with cardiac injury. Importantly, the acute inflammatory response appears to be modulated in those that engage in habitual exercise over time, but it remains unclear if this has a causative role in the reduction in cardiovascular risk observed in individuals who engage in frequent exercise. Those with underlying cardiovascular disease such as coronary artery disease or cardiomyopathies have the highest risk of acute events, and these individuals should undergo careful medical assessment prior to exercise recommendations. A gradual and habitual training prescription, early recognition and reporting of cardiac symptoms and adequate recovery are some strategies that may reduce the risk. The data for prevention of acute cardiovascular events triggered by exercise and the role of inflammation remains incomplete and future investigators may wish to explore: exercise types associated with acute cardiovascular events, the role of strategies to mitigate these risks and role of inflammatory markers.

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